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Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

February 27 2001

Jonca Bull, MD
Acting Director, Division of Anti-Inflammatory, Analgesic
And Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard HFD-550
Rockville, MD 20857

Re: **NDA # 13-217/S-036 SKELAXIN (metaxolone) Tablets 400 mg**

Dear Dr. Bull,

This communication is a follow-on to our letter of February 16 2001 in which we stated that we would be providing the Agency with data that was the basis for our conclusion that there is no correlation between the in vitro dissolution profile of metaxolone tablet preparations and their corresponding in vivo pharmacokinetic profiles.

In the first document, "Determination of the drug substance equilibrium solubility classification of metaxolone under physiological pH conditions"; we provide data on the equilibrium aqueous solubility of metaxolone, the active ingredient in SKELAXIN* as determined according to the FDA Guidance document entitled "Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System" (August 2000).
The results of this study clearly demonstrate that metaxolone is classified as a low solubility drug.

In the second document, "Bioavailability of metaxolone formulations as assessed by *in vitro* dissolution compared to *in vivo* pharmacokinetic profiles" we provide the results of our preliminary investigation into the *in vitro* dissolution profiles of two different tablet formulations of metaxolone compared to SKELAXIN*, together with their corresponding in vivo pharmacokinetic profiles.
The results clearly show that there is not a correlation between the *in vitro* dissolution profile of different tablet formulations of metaxolone and the *in vivo* pharmacokinetic profile.

It was based upon the findings from these two investigations that we have concurred with the Agency that it is important for ourselves, as the originator Company of SKELAXIN® to adequately define the *in vivo* pharmacokinetic profile for the product as well as to provide to the Agency, a more detailed *in vitro* dissolution profile for the tablet presentation that more clearly defines the product. Further supportive data to this effect will be provided for the Agency's review in the near future.

Please feel free to contact me at (650) 553-7187 if you require further information or clarification at this stage.

Sincerely,

Michael C. Scaife

Michael C. Scaife, Ph.D.,
Vice President, Regulatory Affairs

Desk Copies:

E. Dennis Bashaw, Pharm.D.,
Sharon Schmidt, MS

elan
pharmaceutical
technologies

3000 Horizon Drive
King of Prussia, PA 19406

Study Report No: SR-N1257-0001.00

Period Covered: 13Feb-2001 to 016-Feb-2001

Determination Of The Drug Substance Equilibrium Solubility Classification Of Metaxalone Under Physiological pH Conditions

26-Feb-2001

Contributors: S. Wheeler, R. Patel, J. Strasters, J. Bullock

APPROVAL PAGE

Written by: _____ Date: _____

John Bullock
Assistant Director, Analytical Sciences Department

Reviewed by: _____ Date: _____

Shirley Wheeler
Associate , Analytical Sciences Department

Approved by: _____ Date: _____

Jon Swanson
Director, Analytical Sciences & GMP Operations

ABSTRACT

The Analytical Sciences Department Of Elan Pharmaceutical Technologies was requested to determine the equilibrium aqueous solubility of Metaxalone, the active pharmaceutical ingredient (API) in Skelaxin® Tablets, under physiological pH conditions. The objective of this study was to determine the solubility classification of Metaxalone as it relates to the Biopharmaceutical Classification System (BCS). Equilibrium solubility of Metaxalone was determined at 37 °C in a series of pH/buffer media spanning the range from pH 1 to pH 7.4. The solubility of Metaxalone was found to be fairly constant over this pH range averaging about 0.36 mg/mL. Based on the solubility of Metaxalone and considering the highest dose strength (400mg) for Skelaxin® Tablets, Metaxalone is classified as a low solubility API based on the BCS system.

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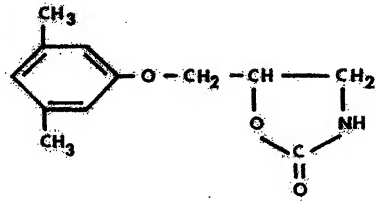
1. *Introduction/Study Objectives*

The Analytical Sciences Department of Elan Pharmaceutical Technologies (EPT) was requested to determine the equilibrium aqueous solubility of Metaxalone, the active pharmaceutical ingredient (API) in Skelaxin® Tablets, under physiological pH conditions. The objective of this study was to determine the solubility classification of Metaxalone as it relates to the Biopharmaceutical Classification System (BCS). The BCS system is used to classify an API based on its aqueous solubility and intestinal permeability properties. This study was focused only on evaluating the aqueous solubility properties of Metaxalone. This was performed at 37 °C in a series of pH/buffer media spanning the pH range from pH 1 to pH 7.4.

The equilibrium aqueous solubility characteristics of Metaxalone were determined using the FDA Guidance Document entitled "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (August 2000) as a guideline. For expediency, a modification was made to the experimental procedure recommended in Section III, subpart A of this FDA guidance. This entailed the use of an ultra-violet spectrophotometric (UV) method in place of a stability-indicating HPLC method for the concentration determination of Metaxalone in the various media. The UV method was adapted from Carnrick Laboratories, Inc. Analytical Method No. S-28-C (Attachment 1) for the dissolution testing of Skelaxin® Tablets.

Solubility determinations were conducted in a total of six media including water, 0.1 M HCl, USP simulated gastric fluid without enzymes (SGF), and aqueous buffers at pH 3.0, 6.8 and 7.4. The FDA guidance states that the number of pH conditions required to accurately define the pH-solubility profile should be based on the ionization characteristics of the API. The structure of Metaxalone provided in Figure 1 reveals that there are no ionizable functional groups for the compound. Thus, the selected pH conditions for this study should adequately characterize the pH-solubility profile of this API. All solubility experiments for this study were conducted at 37 °C with solubility determinations made over the course of 25 hours.

Figure 1 Structure Of Metaxalone



2. *Experimental*

2.1. Batch Description For Bulk Metaxalone API

Technical Information
(refer to Attachment 2 for Certificate of analysis)

2.1.1. Supplier: Roche
2.1.2. Batch No.: MH00095074
2.1.3. Expiry Date: 29-Aug-2005
2.1.4. Assay by HPLC (dried substance): 99.6%
2.1.5. Sum of Impurities: 0.1%

2.2. Instrumentation

2.2.1. **pH meter:** Beckman Model 660
2.2.2. **UV Spectrophotometer:** HP Model 8453 Diode-array UV/Vis
2.2.3. **Dissolution Apparatus:** Distek Model 5100 Dissolution Apparatus

2.3. Buffer Media Preparations

The following media were prepared for conducting the solubility experiments.

2.3.1 **Water:** USP Purified Water
2.3.2 **0.1 M HCL:** For each liter of 0.1M HCL, add 8.3 mL of concentrated HCL to 200 mL of water. Dilute to 1000 mL with water and mix well.

2.3.3 **Potassium Phosphate 0.2 M:** Dissolve 27.22 g of potassium phosphate monobasic (KH_2PO_4) in water, and dilute with water to 1000 mL.

2.3.4 **pH 6.8 Buffer (Potassium Phosphate):** Place 250 mL of 0.2 M Potassium phosphate into an appropriate container. Add 112 mL of 0.2 M NaOH. Then add water to 1000 mL. Mix well. Adjust pH if necessary to 6.8 ± 0.05 with 0.2 M NaOH or 0.2 N Phosphoric acid.

2.3.5 **pH 7.4 Buffer (Potassium Phosphate):** Place 250 mL of 0.2 M Potassium phosphate into an appropriate container. Add 196 mL of 0.2 M NaOH. Then add water to 1000 mL. Mix well. Adjust pH if necessary to 7.4 ± 0.05 with 0.2 M NaOH or 0.2 N Phosphoric acid.

2.3.6 **pH 3.0 Buffer (Potassium Phosphate):** Place 250 mL of 0.2 M Potassium phosphate into an appropriate container. Add about 600 mL of water. Adjust pH to 3.0 with 0.2 N Phosphoric acid. Add water to 100mL.

2.3.7 **Simulated Gastric Fluid (USP):** Dissolve 2.0 g sodium chloride and 7.0 mL of concentrated HCL and sufficient water to make 1000 mL.

2.4. Solubility Determination Protocol

Equilibrium solubility experiments were conducted at 37 °C using a dissolution apparatus equipped with paddles conforming to USP apparatus 2 specifications.

2.4.1. Add about 5g of Metaxalone API to 500mL of the aqueous buffer contained in a dissolution vessel equilibrated at 37°C.

2.4.2. Start a timer and stir solutions at 150rpm.

2.4.3. At selected time points (1, 2, 16.5 and 25 hours) withdraw a 10mL aliqout and filter through a 0.45 micron nylon syringe filter (Gelman 0.45 micron 25mm Acrodisc)

2.4.4. Quantitatively dilute 2.0mL of the filtrate to 10mL with methanol and mix well.

2.5. UV Concentration Test Method

The following is an outline of the UV procedure used to determine the Metaxalone concentration in the various aqueous media.

2.5.1. **Instrumental:**

Wavelength:	280nm
Pathlength:	1cm
Diluent:	80% methanol/water

2.5.2. **Standard Preparations:**

Standard 1: Weigh about 25mg of Metaxalone API into a 250mL volumetric flask. Dissolve with diluent with shaking and/or sonication and dilute to volume. Nominal concentration is 0.1mg/mL

Standard 2: Dilute 10mL of Standard 1 to 25mL with diluent. Nominal concentration is 0.04mg/mL

Standard 3: Dilute 5mL of Standard 1 to 25mL with diluent. Nominal concentration is 0.02mg/mL

Standard 4: Dilute 2mL of Standard 1 to 25mL with diluent. Nominal concentration is 0.008mg/mL

Standard 5: Dilute 1mL of Standard 1 to 25mL with diluent. Nominal concentration is 0.004mg/mL

2.5.3. **Analysis Procedure:**

2.5.3.1. Blank the UV with diluent at 280nm
2.5.3.2. Measure the absorbance of Standards 1-5 at 280nm in triplicate and construct a standard curve.
2.5.3.3. Measure the absorbance of the sample preparations at 280nm in triplicate.

2.5.4. **Calculations:**

Calculate the solubility of Metaxalone in the medium using the following formula:

Solubility in mg/mL = (A smp – Y-int)/m x DF

Asmp = Absorbance of sample at 280nm
Y-int = Y-intercept from the standard curve
m = Slope from the standard curve
DF = Sample dilution factor (10/2 = 5)

3. Data/Results

3.1. Metaxalone UV Calibration Results

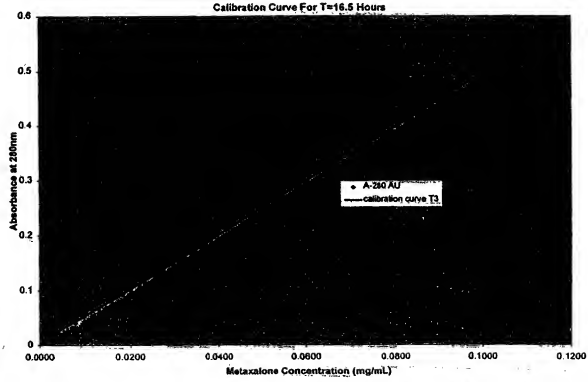
Metaxalone standard UV calibration curves were generated for each of the sampling time points used to determine the Metaxalone solubility for this study (1, 2, 16.5 and 25 hours). In general, the absorbance at 280nm was linear throughout the standard concentration range of 0.004mg/mL to 0.1mg/mL. However, for the first calibration conducted at the one hour time point there was a small amount of curvature at the high end of the concentration range. Therefore, for the one hour time point a second order polynomial fit of the Metaxalone standard data was used. For all of the other standard

curves, a linear fit was used. Table 1 summarizes the regression results for the various standard curves and Figure 2 contains a typical Metaxalone standard response curve using a linear model. The absorbance values for all solubility test samples in the various media were within the range of this standard curve.

Table 1 Summary of Linear Regression Results For The Metaxalone UV Response at 280nm

Regression Statistics	Calibration Curve T=1 Hour	Calibration Curve T=4 Hours	Calibration Curve T=8 Hours	Calibration Curve T=16.5 Hours
Intercept	-0.00903645	0.006104059	0.006665466	0.00970774
X Variable 1	7.190959883	4.961573338	4.895655356	4.82532193
X Variable 2	-19.7814713	NA	NA	NA
Multiple R	0.999964426	0.999737996	0.999674654	0.999675838
R Square	0.999928854	0.99947606	0.999349414	0.999351782
Adjusted R Square	0.999916996	0.999435757	0.999299369	0.999301919
Standard Error	0.001691558	0.004291017	0.004718359	0.004642096
Observations	15	15	15	15

Figure 2 Typical Metaxalone Standard Calibration Curve (T = 16.5 Hours)



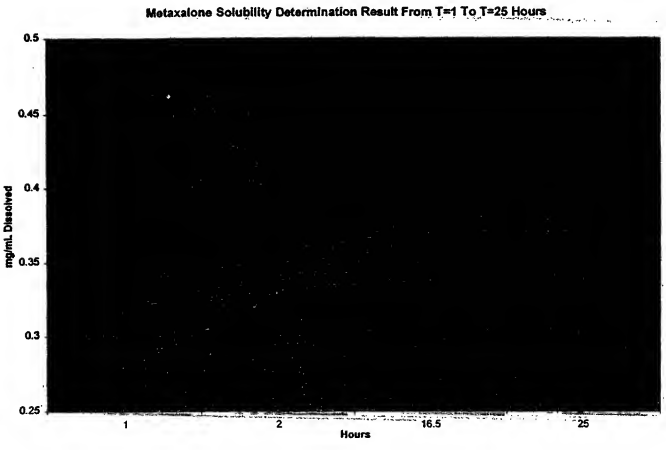
3.2. Metaxalone Equilibrium Solubility Results

Table 2 and Figure 3 summarize the solubility data collected for Metaxalone in the various aqueous media over the course of 25 hours. The consistency in the results between the 16.5 hour point and 25 hour point in all media supports that equilibrium solubility at 37 °C was achieved in all six media. Based on the structure of Metaxalone and the absence of any ionizable functional groups on the molecule, no significant pH dependence in the solubility data was anticipated. This is supported by the data at the 25 hour time point which shows the solubility ranging from 0.34mg/mL to 0.38mg/mL in the different media. The small differences (0.04mg/mL maximum) can be attributed to ionic strength or surface tension differences for the various media. The results obtained in the phosphate buffers at three different pH values were between 0.34-0.35mg/mL. The results obtained in the two acidic media (0.1M HCl and SGF) were 0.37-0.38 mg/mL while in water the result was 0.37mg/mL.

Table 2 Summary Of Metaxalone Equilibrium Aqueous Solubility Data At 37 °C Between pH 1 And pH 7.4

		Solubility Experiment Time In Hours							
		T=1		T=2		T=16.5		T=25	
Medium		Replicate mg/mL	Avg. mg/mL	Replicate mg/mL	Avg. mg/mL	Replicate mg/mL	Avg. mg/mL	Replicate mg/mL	Avg. mg/mL
Water	1	0.3246	0.32	0.3408	0.34	0.3676	0.37	0.3698	0.37
	2	0.3155		0.3407		0.3713		0.3736	
	3	0.3158		0.3404		0.3714		0.3736	
SGF	1	0.3361	0.34	0.3543	0.35	0.3737	0.38	0.3760	0.38
	2	0.3356		0.3524		0.3768		0.3791	
	3	0.3361		0.3536		0.3803		0.3827	
0.1M HCl	1	0.3118	0.32	0.3570	0.36	0.3687	0.37	0.3709	0.37
	2	0.3166		0.3565		0.3719		0.3742	
	3	0.3172		0.3592		0.3717		0.3740	
pH 4.5	1	0.3137	0.32	0.3335	0.33	0.3470	0.35	0.3489	0.35
	2	0.3175		0.3344		0.3465		0.3484	
	3	0.3191		0.3350		0.3466		0.3485	
pH 6.8	1	0.2925	0.29	0.3406	0.34	0.3510	0.35	0.3530	0.35
	2	0.2939		0.3402		0.3543		0.3563	
	3	0.2939		0.3401		0.3536		0.3556	
pH 7.4	1	0.2761	0.28	0.3297	0.33	0.3369	0.34	0.3386	0.34
	2	0.2785		0.3302		0.3392		0.3410	
	3	0.2789		0.3306		0.3395		0.3413	
Equilibrium Solubility (T=25 Hours) Average For All Media									0.36

Figure 3 **Solubility Profiles of Metaxalone At 37 °C As A Function Of Time In Aqueous Media Ranging From pH 1 To pH 7.4**



4. Discussion

The results from this study have confirmed the anticipated lack of a pH dependence of the aqueous solubility of Metaxalone under physiological pH conditions. Within the range of pH 1 to pH 7.4 the average solubility determined for Metaxolone was 0.36mg/mL with a range of 0.34mg/mL to 0.38mg/mL.

In order to determine the solubility classification of Metaxalone according to the BCS system, it is necessary to calculate the volume of aqueous medium sufficient to dissolve the highest dose strength of the drug within the pH range of pH 1 to pH 7.5. To be classified as highly soluble, the highest dose strength must be soluble in ≤ 250mL of

aqueous medium. For Skelaxin® Tablets with a dose strength of 400mg per tablet this equates to a solubility of at least 1.6mg/mL (400mg/250mL) to be considered a highly soluble drug. The highest solubility value that was determined in this pH range for Metaxalone was 0.38mg/mL. Therefore, according to the BCS classification system, Metaxalone is considered a low solubility drug.

5. *Conclusion*

The equilibrium solubility of Metaxalone API was evaluated at 37 °C in aqueous media spanning the range from pH 1 to pH 7.4. The following conclusions can be drawn from this study:

- There is no significant pH dependence to the aqueous solubility of Metaxalone under physiological pH conditions (pH 1 to pH 7.4)
- The average solubility of Metaxalone in this pH range is 0.36mg/mL.
- Considering the aqueous solubility of Metaxalone and the highest dose strength of the Skelaxin® drug product, Metaxalone is classified as a low solubility drug.

6. *References*

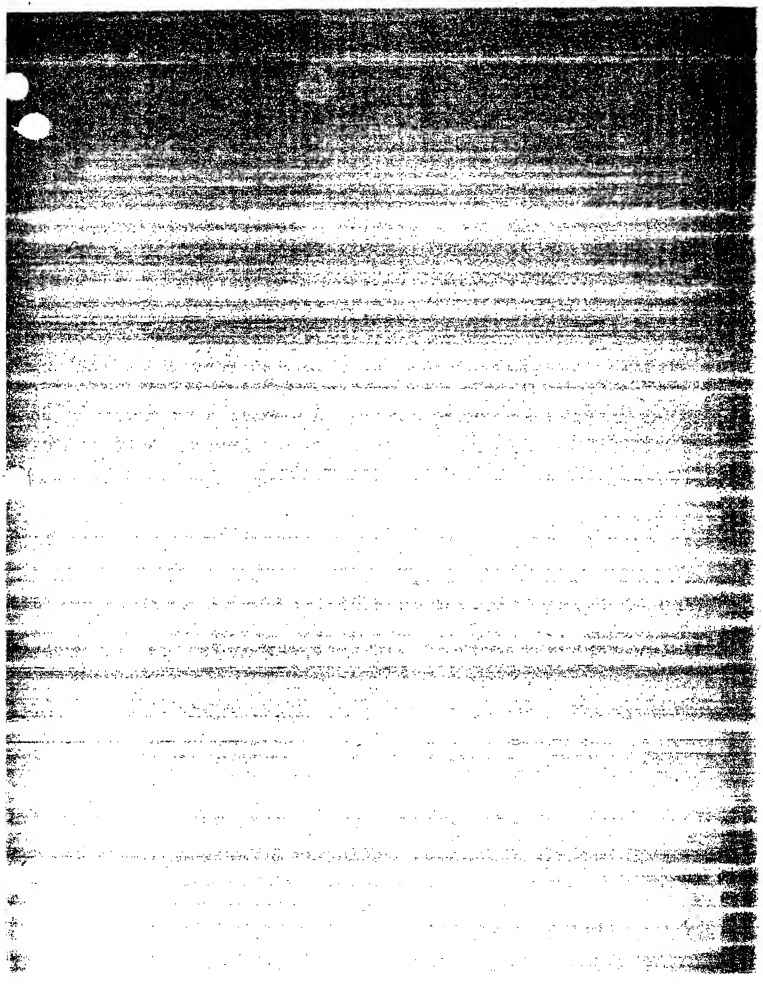
6.1. Laboratory notebook: WHR-5749-159
6.2. Laboratory notebook: JKS-5771-008

7. *Attachments*

7.1. Attachment 1: Carnrick Laboratories, Inc. Analytical Method No. S-28-C
7.2. Attachment 2: Roche Certificate of analysis Metaxalone batch MH00095074

Attachment 1: Carnrick Laboratories, Inc. Analytical Method No. S-28-C

Attachment 2: Roche Certificate of analysis Metaxalone batch MH00095074



élan
pharmaceuticals

Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

Bioavailability of metaxolone formulations as assessed by *in vitro* dissolution compared to *in vivo* pharmacokinetic profiles.

Executive Summary

Pharmaceutical equivalents of poorly soluble drugs, such as metaxalone, and/or slowly dissolving immediate release (IR) solid dosage forms, such as Skelaxin, have potential bioequivalence problems which may be due to differences in drug dissolution in-vivo. In the absence of a validated in vivo / in vitro correlation, comparability of in-vitro dissolution profiles does not indicate in-vivo bioequivalence for such products.

Two studies undertaken to assess the in-vivo performance of pharmaceutical equivalents to Skelaxin confirmed the lack of predictability of in-vitro dissolution for in-vivo bioavailability for metaxalone formulations. The first study evaluated a tablet formulation (BB5800040) that released faster in-vitro than Skelaxin, using a standard dissolution test for a formulation of a poorly soluble drug (water with SLS, USP II@75rpm), but had significantly reduced bioavailability compared to Skelaxin. The second study evaluated a tablet formulation (BB5800047) that had a slightly slower dissolution than Skelaxin at a couple of timepoints, using the same standard dissolution method, but had greatly enhanced bioavailability compared to Skelaxin. Dissolution of these same formulations using lower agitation and less surfactant found that the first formulation (BB5800040) was slower in-vitro to Skelaxin, somewhat reflecting in-vivo performance, but the second formulation (BB5800047), which showed greatly enhanced bioavailability compared to Skelaxin in-vivo, was similar in terms of in-vitro performance to Skelaxin.

These data therefore confirm the lack of predictability of in-vitro dissolution for potential in-vivo bioavailability and bioequivalence problems with formulations of metaxalone and provides compelling evidence that in-vitro dissolution cannot be used as a surrogate for in-vivo performance of pharmaceutical equivalents of Skelaxin.

Bioavailability of metaxolone tablet formulations as assessed by in vitro dissolution compared to in vivo pharmacokinetic profiles.

Background

Metaxalone is a poorly soluble drug (highest dose strength (400mg) not soluble in 250ml aqueous media) and Skelaxin is a slowly dissolving IR solid oral dosage form (<85% dissolved in 30 minutes). Pharmaceutical equivalents of poorly soluble drug products and/or slowly dissolving IR products have potential bioequivalence problems which may be due to differences in drug dissolution in-vivo. In the absence of a validated in vivo / in vitro correlation, comparability of in-vitro dissolution profiles does not indicate in-vivo bioequivalence for such products.

In-vitro and in-vivo evaluation of Skelaxin and pharmaceutical equivalents.

Two studies (summarised below) were undertaken to assess the in-vivo performance of pharmaceutical equivalents to Skelaxin. The dissolution method for release of these formulations was paddles (USP II) at 75rpm, using 1000ml water with 2% SLS, in order to ensure sink conditions.

Study PP99-466

Study Design

This study was a two-treatment, two-period crossover study undertaken in 36 healthy volunteers (38 enrolled, 36 completed). A single oral 400mg tablet dose of metaxalone (Lot # BB5800040) or Skelaxin (Lot # GS639A) was administered in a randomised manner in each treatment period. There was a 7-day washout between treatments. Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36 and 48 hours after dosing.

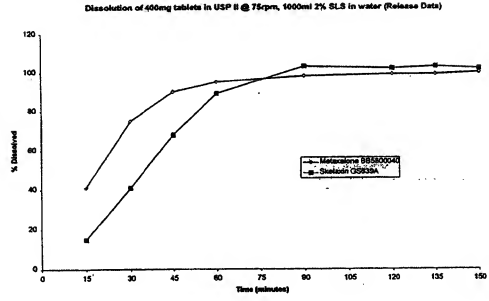
In-vitro dissolution

The In-vitro dissolution test for release was performed on twelve tablets of metaxalone (Lot # BB5800040) and Skelaxin (Lot # GS639A) using USP II (paddles) at 75rpm. 1000ml of an aqueous media containing 2% SLS was used to ensure the achievement of sink conditions. Samples were analysed at 15, 30, 45, 60, 90, 120, 135 and 150 minutes. Both products were similar in terms of potency (metaxalone Lot # BB5800040 : 102.3% ; Skelaxin Lot # GS639A : 99.6%). The dissolution of the test product (BB5800040) was faster than the dissolution of the reference product (Lot # GS639A) at 15, 30, 45 and 60 minutes (Table 1, Figure 1).

Table 1
Dissolution of 400mg tablets in USP II @ 75rpm, 1000ml 2% SLS in water
(Release Data)

Time	Metaxalone BB5800040			Skelaxin GS639A		
Minutes	% Diss.	% CV	Range	% Diss	% CV	Range
15	41	35	20-62	15	6	13-17
30	75	23	48-91	41	4	38-44
45	90	9	75-96	68	5	63-73
60	95	3	90-98	89	3	85-95
90	98	1	96-100	103	4	98-114
120	99	1	97-101	102	1	98-104
135	99	2	97-102	103	2	97-106
150	100	2	97-102	102	2	97-104

Figure 1



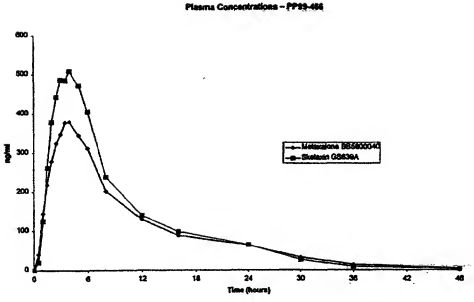
In-vivo performance

Thirty-five of the thirty-six subjects completing the study are included in the analysis. Subject 10 was not included in the analysis as there was analytical interference in both the original and reanalysed data for this subject. In contrast to the faster dissolution of metaxalone Lot # BB5800040 compared to Skelaxin Lot # GS639A, using the referenced dissolution method for release, the Cmax and AUC of this metaxalone formulation were significantly lower than that for Skelaxin (Table 2, Figure 2).

Table 2
Pharmacokinetic Parameters – PP99-466

Parameter	Metaxalone BB5800040 Mean (CV%)	Skelaxin GS639A Mean (CV%)	Ratio		
			Mean	% CV	Range
Cmax (Ln)Cmax 90% CI	518 (59) 425 56-85	669 (39) 620	84	68	14-285
AUC (Ln)AUCt 90%CI	4365 (48) 3932 75-90	5215 (35) 4784	86	30	37-135
AUCinf (Ln)AUCinf 90% CI	4569 (44) 4196 77-93	5074 (34) 4939	89	32	37-158
Tmax	4	3			
T1/2	8	7			

Figure 2



Summary

The in-vitro dissolution of metaxalone Lot # BB5800040, a pharmaceutically equivalent formulation to Skelaxin was faster than the in-vitro dissolution of Skelaxin Lot # GS639A using the dissolution method for release. However, the in-vivo evaluation found metaxalone Lot # BB5800040 to have a lower Cmax and AUC than Skelaxin Lot # GS639A. Therefore the in-vitro dissolution using the dissolution method for release was not predictive of in-vivo performance for the pharmaceutical equivalents evaluated in this study.

Study PP99-642

Study Design

This study was a two-treatment, two-period crossover study undertaken in 46 healthy volunteers (48 enrolled, 46 completed). A single oral 400mg dose of metaxalone (Lot # BB5800047) or Skelaxin (Lot # GS639A) was administered in a randomised manner in each treatment period. There was a 14-day washout between treatments. Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 30, 36 and 48 hours after dosing.

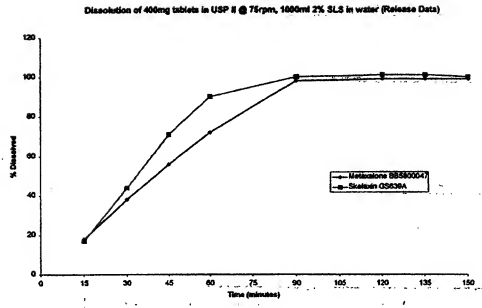
In-vitro dissolution

The In-vitro dissolution test for release was performed on twelve units of metaxalone (Lot # BB5800047) and Skelaxin (Lot # GS639A) using USP II (paddles) at 75rpm. 1000ml of an aqueous media containing 2% SLS was used to ensure the achievement of sink conditions. Samples were analysed at 15, 30, 45, 60, 90, 120, 135 and 150 minutes. Both products were similar in terms of potency (metaxalone Lot # BB5800047 : 100% ; Skelaxin Lot # GS639A : 99.9%). The dissolution of the test product (BB5800047) was slightly slower than the dissolution of the reference product (Lot # GS639A) at 45 and 60 minutes (Table 3, Figure 3).

Table 3
Dissolution of 400mg tablets in USP II @ 75rpm, 1000ml 2% SLS in water (Release Data)

Time	Metaxalone BB5800047			Skelaxin GS639A		
Minutes	% Diss.	% CV	Range	% Diss	% CV	Range
15	18	6	17-21	17	7	15-18
30	38	4	35-40	44	4	41-47
45	56	4	52-60	71	4	67-78
60	72	5	65-78	90	2	87-94
90	98	1	95-99	100	1	98-101
120	99	1	97-100	101	1	99-102
135	99	1	98-100	101	1	99-103
150	99	1	97-99	100	1	99-101

Figure 3



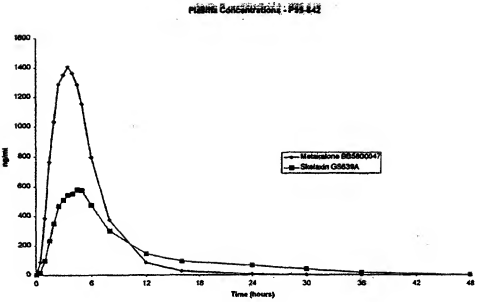
In-vivo performance

Twenty-four of the forty-six subjects completing the study are included in the analysis. Samples from only 30 subjects were analysed on the sponsor's request. Data for subjects 5-8 are not included in the analysis due to poor chromatography and interference and the bioanalysis for subjects 27 and 28 was stopped due to a retention time shift. In contrast to the slightly slower dissolution of metaxalone Lot # BB5800047 compared to Skelaxin Lot # GS639A, using the referenced dissolution method for release, the Cmax and AUC of this metaxalone formulation were significantly higher than that for Skelaxin (Table 4, Figure 4).

Table 4
Pharmacokinetic Parameters – PP99-642

Parameter	Metaxalone BB5800040 Mean (CV%)	Skelaxin GS639A Mean (CV%)	Ratio		
			Mean	% CV	Range
Cmax (Ln)Cmax 90% CI	1798 (37) 1669 202-266	777 (39) 721	250	43	119-574
AUC (Ln)AUCt 90%CI	8138 7428 129-161	5672 5162	151	49	84-258
AUCinf (Ln)AUCinf 90% CI	8223 7518 124-154	5956 5453	144	45	81-228
Tmax	3	3			
T1/2	2	8			

Figure 4



Summary

The in-vitro dissolution of metaxalone Lot # BB5800047, a pharmaceutically equivalent formulation to Skelaxin was slightly slower than the in-vitro dissolution of Skelaxin Lot # GS639A, using the dissolution method for release. However, the in-vivo evaluation found metaxalone Lot # BB5800047 to have a higher Cmax and AUC than Skelaxin Lot # GS639A. Therefore the in-vitro dissolution using the dissolution method for release was not predictive of in-vivo performance for the pharmaceutical equivalents evaluated in this study.

Evaluation of alternative dissolution methodologies

The in-vitro dissolution using the dissolution method for release (USP II, 75rpm, 1000ml water with 2% SLS) was not predictive of the in-vivo performance of Skelaxin and two pharmaceutically equivalent products (Lot # BB5800040 and BB5800047). Figures 5 and 6 summarise the in-vitro and in-vivo performance of these formulations.

The in-vitro and in-vivo performance of Skelaxin was similar for the two studies. Metaxalone Lot # BB5800040 was faster in-vitro than Skelaxin and showed a loss in bioavailability in vivo compared to Skelaxin. Metaxalone Lot # BB5800047 was slower in-vitro than Skelaxin and was superbioavailable in-vivo compared to Skelaxin.

Figure 5

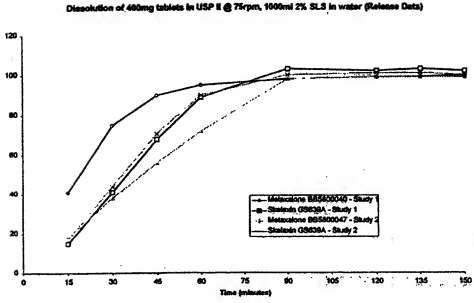
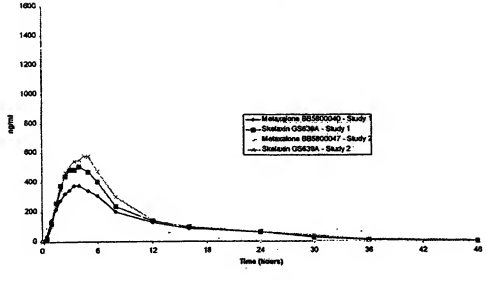


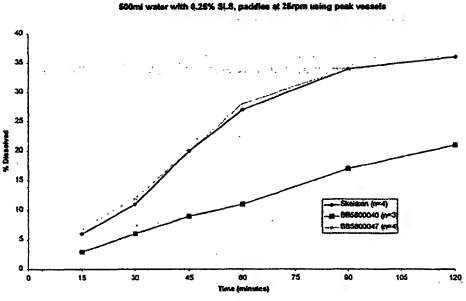
Figure 6



The in-vitro performance of Skelaxin and the pharmaceutically equivalent metaxalone formulations were evaluated using an alternative dissolution medium (500ml water with 0.25% SLS, paddles at 25rpm using peak vessels) to determine if this dissolution system might be capable of predicting the in-vivo performance of these formulations. This method was chosen as it was considered less severe in terms of agitation and surfactant concentration and the volume of media was lower, which might better reflect in-vivo conditions.

Figures 7 summarises the dissolution of the three formulations using this method. Approximately three units were evaluated in each case.

Figure 7



Summary

This data shows that there is a significant impact of both agitation and surfactant concentration on the release of metaxalone from Skelaxin and the pharmaceutically equivalent metaxalone formulations. The impact of the dissolution conditions affects the three formulations differently. Lot # BB5800047 was found to be comparable to Skelaxin which is not the case in-vivo, while the dissolution of Lot# BB5800040 better reflected the in-vivo performance.

Conclusions

The data presented indicates that in-vitro dissolution using standard dissolution methods is not predictive of in-vivo performance for pharmaceutically equivalent formulations of Skelaxin, the slowly dissolving IR solid dosage form of the poorly soluble drug metaxalone. In addition, altering the dissolution conditions alters the comparative performance of these formulations. As dissolution appears to be dependent on formulation or process parameters, dissolution conditions that achieve an in vivo / in vitro correlation for these formulations, might not be appropriate for predicting the in-vivo performance of alternative formulations. This data therefore provides compelling evidence that in-vitro dissolution cannot be used as a surrogate of in-vivo performance for pharmaceutical equivalents of Skelaxin.